

Addressee's fax number: 1-703-308-6459

WORLD INTELLECTUAL PROPERTY ORGANIZATION (WIPO)
ORGANISATION MONDIALE DE LA PROPRIÉTÉ INTELLECTUELLE (OMPI)



PCT

(Patent Cooperation Treaty)

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Date : 29 August 2000 (29.08.00) Fax: 1-703-308-6459

**To : Assistant Commissioner for Patents
In its capacity as Elected Office
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE**

RECEIVED

29 AUG 2000

**Legal Staff
International Division**

Attention: Dan Stemmer, PCT Legal Office

From : Ting Zhao

Telephone: (41-22) 338 9749

Email address: ting.zhao@wipo.int

Concerns: PCT/EP96/05846

Number of pages including cover sheet : 13

Dear: Dan Stemmer, PCT Legal Office

As requested by your email of 25 August 2000, enclosed please find copies of the Request Form, Form PCT/IB/310 and the IPER.

With best regards,

Ting Zhao
PCT Examination Section

A handwritten signature in black ink, appearing to be 'Ting Zhao', is written over the printed name.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 96 / 0 584 6

International Application No.

27 DEC 1996

International Filing Date

(27. 12. 96)

EUROPEAN PATENT OFFICE

PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) BSS.001

Box No. I TITLE OF INVENTION PRODUCT DERIVED FROM MILK SUBSTANTIALLY FREE OF BETA CASEIN FROM NON-HUMAN MAMMALS AND RELATIVE USE

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BIOSISTEMA di Pier Luigi Sarapani & C. Sas
Via Per Luco dei Marsi
67051 AVEZZANO (Prov. of L'AQUILA)
ITALY

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (i.e. country) of nationality:
ITALY

State (i.e. country) of residence:
ITALY

This person is applicant
for the purposes of:

☐ all designated
States

☒ all designated States except
the United States of America

☐ the United States
of America only

☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POZZILLI Paolo
Via Vallombrosa, 40
00135 ROME - ITALY

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box
is marked, do not fill in below.)

State (i.e. country) of nationality:
ITALY

State (i.e. country) of residence:
ITALY

This person is applicant
for the purposes of:

☐ all designated
States

☐ all designated States except
the United States of America

☒ the United States
of America only

☐ the States indicated in
the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

GERVASI Gemma
c/o NOTARBARTOLO & GERVASI
Corso di Porta Vittoria, 9
20122 MILAN - ITALY

Telephone No.

Facsimile No.

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Mold va, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakstan | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| <input checked="" type="checkbox"/> LR Liberia | |
| <input checked="" type="checkbox"/> LS Lesotho | <input checked="" type="checkbox"/> BA Bosnia and Herzegovina |
| <input checked="" type="checkbox"/> LT Lithuania | <input checked="" type="checkbox"/> CU Cuba |
| <input checked="" type="checkbox"/> LU Luxemb urg | <input checked="" type="checkbox"/> LC Saint Lucia |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Sheet No. ...3...

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Box No. VI PRIORITY CLAIMFurther priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) ITALY	27th December 1995 (27. 12. 95)	RM95A000850	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):
Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.

Country (or regional Office):

Date (day/month/year):

Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request : 3 sheets
 2. description : 17 [13] sheets
 3. claims : 4 sheets
 4. abstract : 1 sheets
 5. drawings : 2 sheets

Total : 29 [29] sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
 2. ☐ copy of general power of attorney
 3. ☐ statement explaining lack of signature
 4. ☐ priority document(s) identified in Box No. VI as item(s)
 5. ☐ fee calculation sheet
 6. ☐ separate indications concerning deposited microorganisms
 7. ☒ nucleotide and/or amino acid sequence listing (diskette) STATEMENT
 8. ☒ other (specify): accompanying letter

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Milan, Italy, December 20, 1996

GERVASI Gemma

For receiving Office use only		2. Drawings: <input checked="" type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:	27 DEC 1996 (27. 12. 96)	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority specified by the applicant: ISA /	6. <input checked="" type="checkbox"/> Transmittal of search copy delayed until search fee is paid	

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	04 FEBRUARY 1997 (04. 02. 97)

File copy

PCT/EP96/05846

PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
DOCUMENT TRANSMITTED

To:

AU,BR,CA,CN,CZ,DE,EP,GB,IL,JP,
KP,KR,NO,NZ,PL,RO,RU,SK,US

in its capacity as elected Office

Date of mailing (day/month/year)

17 April 1998 (17.04.98)

International application No.

PCT/EP96/05846

International filing date (day/month/year)

27 December 1996 (27.12.96)

Applicant

MIDIA LIMITED et al

The International Bureau transmits herewith the following documents and number thereof:

_____ copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Christelle Croci

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

RECD	14 APR 1998
WIPO	PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BSS.001	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 96/ 05846	International filing date (day/month/year) 27/12/1996	Priority date (day/month/year) 27/12/1995
International Patent Classification (IPC) or national classification and IPC C07K14/47		
Applicant MIDIA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


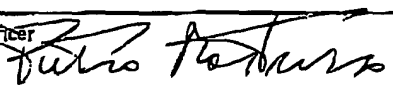
2. This **REPORT** consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 3 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 16/07/1997	Date of completion of this report 09.04.98
Name and mailing address of the IPEA  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3018	Authorized officer  Telephone No. (020-4120)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP96/05846

1. Basis of the report

1. This report has been drawn up on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*

☐ the international application as originally filed

☒ the description, pages 1-17, as originally filed
 pages, filed with the demand
 pages, filed with the letter of

☒ the claims, Nos. , as originally filed
 Nos. , as amended under Article 19
 Nos. , filed with the demand
 Nos. 1-15, filed with the letter of January 7, 1998

☒ the drawings, sheets / fig. 1/2 to 2/2, as originally filed
 sheets / fig. , filed with the demand
 sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.
☐ the drawings, sheets / fig.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP96/05846

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Claims	1-9, 11-17	YES
	Claims	10	NO
Inventive Step	Claims	1-9, 11-17	YES
	Claims	10	NO
Industrial Applicability	Claims	1-17	YES
	Claims		NO

2. Citations and Explanations

Claims 1-9 and 11-17 cover new matter and are therefore admissible under Art. 33(1) PCT. In fact no milk or milk-derived product has been proposed for prevention of insulin-dependent diabetes (IDD). Instead it is considered that the wording of claim 10 is insufficient to distinguish its subject matter from the prior art. Therefore claim 10 is objectionable under Art. 33(2) PCT. In consideration of the disclosure 1 to 6, the objective problem underlying the present application is considered to reside in the provision of alternative products useful in the prevention of IDD. The applicant has submitted no proof that milk derivatives lacking determined beta-casein sequences can be useful in the prevention of IDD; however this assumption can be held as tenable in consideration of the document Lancet 348, pages 926-928 (1996).

Even though the prior art mentions milk derivatives depleted in β -casein, no hint is provided about a relation of this protein or some of its specific subsequence with IDD.

Therefore claims 1-9, 11-17 can be considered to possess an inventive step under Art. 33(3) PCT.

Claims 1-17 are provided with industrial applicability under Art. 33(4) PCT.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP96/05846

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application no. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-9636239 (McLachlan)	21-11-1996	9-5-1996	16-5-1995
WO-A-9614577 (The National Child Research Foundation et al.)	17-5-1996	3-11-1995	4-11-1994

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP96/05846**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 10, containing a reference to milk enriched in β -casein for use in prevention of IDD, is considered to be contradictory with the other claims. In fact the starting point of the present application is the provision of alternative dietary products for prevention of IDD; this disease has been demonstrated to be related to β -casein or to some of its sequences. Claim 10, in its present form, covers also product enriched in unmodified β -casein, which cannot therefore be used for the above purpose.

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CLAIMS

1. Dietary or pharmaceutical products derived from milk, or milk itself, to be used in diets for the prevention of insulin-dependent diabetes substantially free of non-human beta casein.

2. Dietary or pharmaceutical products derived from milk or milk itself, to be used in diets for the prevention of insulin-dependent diabetes, substantially free of beta casein from non-human mammals resulting immunogenic in view of molecular mimicry with the GLUT 2 protein.

3. Dietary or pharmaceutical products derived from milk, or milk itself, to be used in diets for the prevention of insulin-dependent diabetes, substantially free of beta casein from non-human mammals resulting immunogenic due to molecular mimicry with the protein GLUT2 and to which non-immunogenic beta caseins selected among the animal, vegetable and/or synthetic ones and mixtures thereof have been added.

4. Dietary or pharmaceutical products derived from milk, or milk itself, to be used in diets for the prevention of insulin-dependent diabetes, substantially free of caseins comprising the sequence: Pro-Gly-Pro-Ile-His (SEQ ID NO:1) or Pro-Gly-Pro-Ile-Pro (SEQ ID NO:2) or the sequences comprising them: Ser-Leu-Val-Tyr-Pro-Phe-Pro-Gly-Pro-Ile-His-Asn (SEQ ID NO:3) or Ser-Leu-Val-Tyr-Pro-Phe-Pro-Gly-Pro-Ile-Pro-Asn (SEQ ID NO:4).

5. Dietary or pharmaceutical products derived from milk, or milk itself, to be used in diets for the prevention of insulin-dependent diabetes comprising caseins which do not present the sequence: Pro-Gly-Pro-Ile-His (SEQ ID NO:1) or Pro-Gly-Pro-Ile-Pro (SEQ ID NO:2), said caseins being selected among those in which:

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- some or all of the amino acids in the said sequences are modified;
- the said sequences are removed;
- the said sequences are substituted by the homologous sequence in human beta casein and related mixtures.

6. Dietary or pharmaceutical products derived from milk, or milk itself, to be used in diets for the prevention of insulin-dependent diabetes comprising caseins presenting the sequence Val-Glu-Pro-Ile-Pro (SEQ ID NO:5) or a longer sequence comprising it: Ser-Leu-Val-Tyr-Pro-Phe-Val-Glu-Pro-Ile-Pro-Tyr (SEQ ID NO:6).

7. Product according to claims 1-6 and integrated with vegetable, animal and/or synthetic beta caseins with peptides derived from the hydrolysis of animal, vegetable and/or synthetic proteins lacking the sequence Pro-Gly-Pro-Ile-His (SEQ ID NO:1) or Pro-Gly-Pro-Ile-Pro (SEQ ID NO:2) and mixtures thereof.

8. Dietary or pharmaceutical products derived from milk, or milk itself, to be used in diets for the prevention of insulin-dependent diabetes comprising caseins in which beta casein is lacking the amino acid sequence Gly-Pro-Ile-His (SEQ ID NO:7) or Gly-Pro-Ile-Pro (SEQ ID NO:8) because it has been produced by animal species genetically not producing proteins with such a sequence.

9. Milk naturally lacking beta casein, produced by genetically modified animals, to be used in diets for the prevention of insulin-dependent diabetes.

10. Milk containing human beta casein obtained from genetically manipulated microorganisms or animals, to be used in diets for the prevention of insulin-dependent diabetes.

11. Process to obtain a dietary product according to claim 5 in which

- 16 -

the amino acid sequences are modified via application of techniques such as genetic engineering and biological cross-selection.

12. Use of beta casein or peptide fragments not demonstrating molecular mimicry with the protein GLUT2 for the preparation of dietary or pharmaceutical products for the prevention of insulin-dependent diabetes.

13. Use of beta casein or peptide fragments according to claim 12 for preparing a food dietary or pharmaceutical product for the prevention of insulin-dependent diabetes.

14. Use of caseins according to any of the claims 5-8 for preparing a food dietary or pharmaceutical product for the prevention of insulin-dependent diabetes.

15. Use of milk according to claims 9-10 for preparing a food dietary or pharmaceutical product for the prevention of insulin-dependent diabetes.

* * RX REPORT ***
* *****

RECEPTION OK

TX/RX NO	6194
CONNECTION TEL	41 22 740 14 35
CONNECTION ID	PCT EXAM SECTION
START TIME	08/29(TU)09:15
USAGE TIME	06'35"
PGS.	13
RESULT	OK